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EXAMINER	
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ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,357	BARU ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _10 April 2009_.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _28-42,45,47,50,53,54 and 57-74_ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _28-42,45,47,50,53,54 and 57-74_ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The instant Office action replaces the non-final rejection mailed April 14, 2009.

Amendment after FINAL rejection filed March 6, 2009 is acknowledged. Upon reconsideration, the finality sent out on January 6, 2009 is withdrawn, and the case is hereby reopened. The indication of allowability of claims 45 and 53 are hereby withdrawn. Claims 1-27, 43-44, 46, 48-49, 51-52, 55-56 have been cancelled and new claims 58-74 have been added. Claims 28-42, 45, 47, 50, 53-54 and 57-74 are pending in this application.

Applicant elected without traverse of species G-CSF for protein and multiple sclerosis as the disease in the reply filed on June 11, 2007. Upon further review, restriction requirement is hereby withdrawn. All withdrawn claims are hereby rejoined. **Claims 28-42, 45, 47, 50, 53-54 and 57-74 are examined on the merits in this office action**. A Non-final office action follows below.

Withdrawn Rejections

1. Claims 28-42, 46-51, 54-56 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description, is hereby withdrawn in view of Applicant's amendment to the claims.

2. Claims 28-32, 36-37, 39-42, 46, and 55-56 rejected under 35 U.S.C. 102(b) as being anticipated by Baru M (WO 99/55306, filed in the IDS 2/15/2006), is hereby withdrawn in view of Applicant's amendment to the claims.

3. Claims 44, 46-50, 54-56 rejected under 35 U.S.C. 112, first paragraph, as not enabling, is hereby withdrawn in view of Applicant's amendment to the claims.

4. Claims 28-32, 36-37, 39-42, 46, and 55-57 rejected under 35 U.S.C. 103(a) as being unpatentable over Baru M (WO 99/55306, filed in the IDS 2/15/2006), is hereby withdrawn in view of Applicant's arguments and amendment to the claims.

New Objections to the Specification

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see page 10, line 28). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

6. The use of the trademark COPAXONE® (page 4, lines 15 and 20 and page 9, lines 7, 9, and 12, etc.) has been noted in this application throughout the specification and claims, for example, 28, 47, 50, 53, 57, 59, 64, 73-74. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Moreover, since Applicants have provided the sequence of Copaxone in the sequence listing, the SEQ ID NO must accompany the name wherever is appears throughout the specification and the claims. Appropriate correction is required.

New Claim Objections

7. Claim 65 is objected to for the following minor informality: claim 65 recites, "The pharmaceutical composition of claim 63, wherein the amphipathic lipid is selected from…" There appears to be an error in the claim dependency. Claim 65 appears to more properly depend from claim 64, not claim 63; this inadvertent error was confirmed with Applicant. Therefore, claim 65 is objected to. For the purpose of examination, claim 65 will be examined as it depends on claim 64. Appropriate correction is required.

Rejection-35 U.S.C. § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 64 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This is a new matter rejection. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the claimed invention.

The claims are drawn to a pharmaceutical composition for parenteral administration, comprising a therapeutically effective amount of a protein or polypeptide selected from…and one or more colloidal particles comprising approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer, wherein the protein or polypeptide is non-covalently bound to one or more colloidal particles. The instant claim encompasses both

encapsulated and non-encapsulated protein/polypeptides since the limitation to be non-encapsulated is absent (Note: all other claims contain this non-encapsulated limitation). Since only non-encapsulated protein/polypeptides were disclosed in the original claims and the specification as filed, the lack of this limitation broadens the claimed genus to include that which was not originally disclosed.

Lack of Ipsis Verbis Support

9. The specification is void of any literal support for the claimed genus. In the context of all colloidal particles, the only embodiments claimed and disclosed are those *not* encapsulated in the colloidal particles. The specification does not disclose the broader genus of any colloidal particles currently claimed in claim 64 (i.e., absent the limitation of non-encapsulated). The genus includes species other than not encapsulated ones. Thus, there is no literal support found in original claim or specification for this genus of all colloidal particles now claimed.

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Lack of Implicit or Inherent Support

10. "While there is not in *haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." See MPEP 2163. Thus support can be furnished implicitly or inherently for a specifically claimed limitation. However, the specification lacks any implicit or inherent support for the claimed genus of all colloidal particles. As explained supra, there is no support for the concept of a genus of all colloidal particles in the specification. Since the limitation "is not encapsulated in colloidal particles" have been removed, this broadens the claims to include a genus of all colloidal particles. There is no inherent or implicit support, because other species of colloidal particles, other than those non-encapsulated, have not been contemplated.

Rejection-35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 64, 65, and 67-68 are rejected under 35 U.S.C. 102(b) as being anticipated by Allen et al (US Patent No. 5,527,528).

Allen et al teach a method of attaching a targeting protein to a polyethylene glycol (PEG) coated liposome by non-covalent binding to the outer surface of the liposome (see FIG 1A; Col. 4, lines 20-27), by conjugating the antibody to a spacer chain such as PEG (see FIG 2B; Col. 4, lines 40-50), or by biotinylation of the antibody and specific, high affinity, non-covalent binding to avidin that is bound to the liposome surface (see FIG 1C; Col. 2, lines 32-42) and Col. 9, lines 55-67; FIG 5, Col. 17, lines 25-55). Allen teaches a pharmaceutical composition comprising a therapeutically effective amount of a protein and neutral colloidal particles that are approximately 1-20 mol percent of an amphipathic lipid derivatized with PEG (see Col. 8, lines 57-59; Col. 9, line 20). Additionally, the reference teaches that liposome compositions are typically prepared with lipid components present in a molar ratio of about 30-75% vesicle-forming lipids, 25-40% cholesterol, 1-20 % polymer derivatized lipid, and 0.01-10 mole percent of lipid derivatized employed for antibody coupling. One exemplary liposome formulation includes hydrogenated soy phosphatidylethanoloamine (HSPE), cholesterol (CH), DSPE-PEG at a molar ratio of 2:1:0.1 (see Col. 8, lines 57-64). The protein is a targeting antibody that is capable of externally binding the colloidal particle (see FIG 5, Col. 2, lines 32-42; Col. 9, lines

55-67). The reference further teaches liposome-entrapped compounds, such as peptide hormones, vasopressin, cytokines (interferons alpha, beta, gamma), interleukins and colony stimulating factors (macrophage, granulocyte, granulocyte and macrophage), viral or bacterial vaccines and so on (see Col. 7, lines 18-28). Therefore, the reference anticipates instant claims 64, 65, and 67-68.

Rejection-35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 28-34, 36-42, 57, 59-60, 62-65, 67-68, 73-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baru M (WO 99/55306, filed in the IDS 2/15/2006) in view of Martin et al (US Patent No. 5,225,212) and Ishikawa et al (US Patent No. 5,824,778) and Igari et al (US Patent No. 5,534,269).

Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles. The particles comprise approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer which carries substantially no net charge. Further, Baru teaches that the protein or polypeptide is capable of externally binding the colloidal particles, or is capable of binding polyethylene glycol and is not encapsulated in the colloidal particle (see abstract). Additionally, the reference teaches these formulations extend the half-life of proteins (see abstract) and the reference teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, binds to membranes comprising phosphatidylcholine:phosphatidylserine (PC:PS) (i.e., two amphipathic lipids); non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V (see p.7, lines 6-12, claims 18-19), all of which address the limitations of independent claims 28, 57, 59, 64, 73, and 74 and dependent claim 29. The reference teaches that "the term proteins or polypeptides capable of binding polyethylene glycol includes proteins and polypeptides which

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bind to PEG or derivatives of PEG by any non-covalent mechanism, such as ionic interactions, hydrophobic interactions, hydrogen bonds and Van der Waals attraction (see p. 7, lines 13-18), meeting the limitation of non-covalent interaction.

The reference further teaches that the colloidal particle has a mean particle diameter of between about 0.05 to about 0.4 microns, and approximately 0.1 microns (see claims 2-3), which meets the limitation of claims 30-31 and 59.

The reference further teaches that the amphipathic lipid is a phospholipid from natural or synthetic sources (see claim 4), which meets the limitation of claims 32 and 36.

The reference teaches the polyethyleneglycol-phosphatidyl ethanolamine (PEG-PE) preparation (see p. 6, lines 19-20), meeting the limitation of claims 33, 60, 62, 63, 65, 67-68, and 74.

Additionally, the reference teaches distearoyl phosphatidyl-ethanoloamine methyl PEG 2000 (DSPE-PEG 2000), meeting the limitation of claim 34.

The reference further teaches that the biocompatible hydrophilic polymer is selected from group consisting of polyalkylether, polylactic and polyglycolic acid families, and is a polyethylene glycol (see claims 6-7), which meets the limitations of claims 39-40.

The reference further teaches that the polyethylene glycol has a molecular weight of between about 1000 to about 5000 daltons (approximately 2000 daltons) (see claims 8-9), which meets the limitations of claims 41-42.

The reference further teaches that "phospholipids used are synthetic and non-toxic, and can therefore, be used in vivo for therapeutic treatment…liposomes do not encapsulate FVIII, so that smaller sized liposomes can be used which have a longer half-life *in vivo*, since they are not

removed by the reticuloendothelial system (RES) (see p. 4, lines 1-6). Since non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V, this meets the limitation of other proteins. The reference teaches the treatment of blood disorder, such as hemophilia (see claim 14). The reference teaches all of the active method steps of instant claim 57. The active method steps of instant claim is that a pharmaceutical composition for parenteral administration is administered to a patient, wherein the protein or polypeptide is not encapsulated in the colloidal particles. The reference teaches administration of a therapeutically effective amount of a compound to a patient in need thereof (see claim 14), and defines that "the term therapeutically effective amount is to be understood as referring to an amount of FVIII which results in a level of FVIII in the bloodstream having a desired therapeutic effect (see p. 4, lines 14-19). The reference further teaches that liposomes containing E-PC/PEG-PE were the most effective since both the initial FVIII activity and the half-life time were higher for this composition than for Kogenate or Kogenate-liposome mixtures where the liposomes were composed of E-PC/PG or E-PC only (see Table 1, p. 11, lines 3-7).

The difference between the reference and the instant claims is that the reference does not teach the protein or polypeptide G-CSF, GM-CSF, and Interferon gamma, which are species required in claim 28, 57, 59, 64, 73, and 74, and does not teach the composition further comprising a second amphipathic lipid of phosphatidylcholine (PC), as required for Claim 37, or further comprising cholesterol, as required for claims 38 and 73.

Martin et al teach a liposome composition for extended release of a therapeutic compound in to the bloodstream (see abstract). The liposomes are composed of vesicle forming lipids (phospholipids, such as phosphatidylcholine (PC), phosphatidylethanolamine (PE),

phosphatidic acid (PA), phosphatidylinositol (PI) and the like) (see Col. 5, lines 61-66), which teaches limitations of Claim 37. The reference further teaches that the liposomes are between 1-20 mole percent of vesicle-forming lipid derivatized with hydrophilic polymer, having sizes in a selected size range between 0.1 and 0.4 microns, and contain the therapeutic compound in liposome-entrapped form (see abstract). The reference teaches that a biocompatible hydrophilic polymer is PEG having a molecular weight between about 1,000-5,000 daltons, and the polymer is derivatized with the polar head group of phospholipids, such as PE (see Col. 3, lines 1-16 and claims 5 and 6). The reference teaches that these are readily water soluble, can be coupled to vesicle-forming lipids, and are tolerated in vivo without toxic effects (see Col. 5, lines 39-43). The reference further discloses that PEG-liposome has a longer retention time in the blood than the conventional liposomes (see Col. 4, lines 44-46 and Figure 9). The reference teaches that the composition is intended for intravenous administration and the polypeptide may be a peptide or protein, such as superoxide dimutase, **interferons (alpha, beta, and gamma)…colony stimulating factors (M-CSF, G-CSF, GM-CSF)** (see Col. 3, lines 17-41 and claim 9). The reference further teaches supplementation of cholesterol in the composition (see Table 3 and 5), which teaches the limitation of Claim 38. The reference teaches that cholesterol may be less tightly anchored to a lipid bilayer membrane, particularly when derivatized with a high molecular weight polyalkylether, and therefore be less effective in promoting liposome evasion of the RES in the bloodstream (see Col. 6, lines 3-9). Martin teaches that other lipid components, such as cholesterol, are also known to contribute to membrane rigidity and stability in lipid bilayer structures (see Col. 6, lines 32-35).

Ishikawa et al (US Patent No. '778) teaches that "it has been desired to prolong the half-life of human G-CSF in the body as to enhance it s effects, as may be expected. Improvement in biological activity and pharmacokinetics, which may be expected as a result of the modification of human G-CSF by polyethylene glycol is described (see column 1, lines 55-63). Furthermore, Igari et al (US Patent No. '269) teaches that "thanks to advances in genetic engineering and cell engineering technologies, some (proteins) have been produced in large mounts for pharmaceutical application…Such protein pharmaceuticals include interferons (alpha, beta, gamma)...erythropoietin and granulocyte colony-stimulating factor (G-CSF). These proteins, however, since they have generally short biological half-life, must be administered frequently, posing the significant physical burden of injection on patients. To solve this problem, various attempts have been made to develop sustained-release preparations" (see column 1, lines 11-29).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru and Martin, since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V and Martin et al teach Interferon gamma, G-CSF, M-CSF, GM-CSF, and other proteins that are incorporated with the liposomes. Both Ishikawa and Igari teach that protein pharmaceuticals are known to have short half life, including G-CSF, interferon Gamma and other proteins, and various attempts have been developed to develop sustained-release preparation. Therefore, it would have been obvious to one of ordinary skill in the art to

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use the liposomes of Baru to increase the half life of these compounds. One of ordinary skill in the art would have been motivated to combine the teachings, since the prior arts all teach therapeutic composition containing PEG-neutral liposome, and Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which **have a longer half-life in vivo**, because they are not removed by the RES (see p. 4, lines 1-6). Martin reference teaches that these PEG-neutral liposomes are well tolerated in vivo without toxic effects, and that cholesterol contributes to membrane rigidity and stability in lipid bilayer structures and be less effective in promoting liposome evasion of the RES in the bloodstream. The formulations of the prior arts are similar and they achieve the same effect (increasing the half-life of the compound). Furthermore, pegylation of protein is general concept in the protein arts (see Ishikawa). PEGylation of proteins increases half-life of these proteins, including G-CSF, interferon gamma and factor VIII (including prothrombin, factor X and so on disclosed in Baru reference). There is a reasonable expectation of success, since pegylation or utilizing liposomes would increase the half-life of the therapeutic compounds and by not encapsulating the compounds in the liposomes, smaller sized liposomes can be used which have a longer half-life *in vivo*. There is a reasonable expectation that other proteins and peptides known in the art would behave the same way as Factor VIII, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes proteins and polypeptide.

13. Claims 28-34, 36-42, 57, 59-60, 62-65, 67-68, 73-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baru M (WO 99/55306, filed in the IDS 2/15/2006) in view of Martin et al (US Patent No. 5,225,212) and Chen et al (US Patent No. 5,512,549) or Galloway et al (US Patent No. 5,705,483).

The teachings of Baru and Martins are described, *supra*. The difference between the references and the instant claims is that the references do not teach GLP-1.

However, Chen et al teach that “presently, therapy involving the use of GLP-1 type molecules has presented a significant problem because the serum half-life of such peptides is quite short. For example, GLP-1(7-37) has a serum half-life of only 3 to 5 minutes. Presently, the activity of dipeptidyl-peptidase IV (DPP IV) is believed to readily inactivate GLP-1(7-37) in addition to rapid absorption and clearance following parenteral administration. Thus, there exists a critical need for biologically active GLP-1 (7-37) analogs that possess extended pharmacodynamic profiles following parenteral administration" (see column 3, lines 13-22). Galloway also teaches that “the biological half-life of GLP-1 molecules, particularly those molecules which are affected by the activity of dipeptidyl-peptidase IV (DPP IV) is quite short. For example, the biological half life of GLP-1 (7-37) is a mere 3 to 5 minutes (see column 3, lines 41-45), and is further influenced by its rapid absorption following parenteral administration to a mammal. Thus, there also exists a need for a GLP-1 compound which delays absorption following administration” (see column 3, lines 41-48).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru et al, Martins et al patents, Chen et al or Galloway et al, since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective

amount of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V. Martin et al teach Interferon gamma, G-CSF, M-CSF, GM-CSF, and other proteins that are incorporated with the liposomes.

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Furthermore, Chen and Galloway both teach that "there exists a need for a GLP-1 compound that possess extended pharmacodynamic profile (increased half-life) following parenteral administration." Therefore, it would have been obvious to one of ordinary skill in the art to use the liposomes of Baru to increase the half life of these compounds. Therefore, one of ordinary skill in the art would have been motivated to combine the teachings, since the prior arts all teach therapeutic composition containing PEG-neutral liposome, and Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which **have a longer half-life in vivo**, because they are not removed by the RES (see p. 4, lines 1-6). Martin reference teaches that these PEG-neutral liposomes are well tolerated *in vivo* without toxic effects, and that cholesterol contributes to membrane rigidity and stability in lipid bilayer structures and be less effective in promoting liposome evasion of the RES in the bloodstream. The formulations of the prior arts are similar and they achieve the same effect (increasing the half-life of the compound). PEGylation of proteins increases half-life of these proteins, including G-CSF, interferon gamma and factor VIII (including prothrombin, factor X and so on disclosed in Baru reference) and GLP-1. There is a reasonable expectation of success, since pegylation or utilizing liposomes would increase the half-life of the therapeutic compounds and by not encapsulating the compounds in the liposomes,

smaller sized liposomes can be used which have a longer half-life *in vivo*. There is a reasonable expectation that other proteins and peptides known in the art would behave the same way as Factor VIII, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes proteins and polypeptide.

14. Claims 28-34, 36-42, 47, 50, 53, 57, 59-60, 62-65, 67-68, 73-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baru M (WO 99/55306, filed in the IDS 2/15/2006) in view of Martin et al (US Patent No. 5,225,212) and Heldman et al (US 2006/0039962 A1, 102(e) date) as evidenced by (http://www.copaxone.com/, prescribing information, accessed 7/27/2009) and further in view of Braxton SM (US Patent No. 5,766,897).

The teachings of Baru and Martin et al is described, *supra*. The difference between the references and the instant claims is that the reference does not teach Copaxone® and treatment of MS.

However, Heldman et al teach amphiphilic compound capable of forming vesicles or liposomes (see abstract). The reference teaches that the vesicle preparations are designed for delivering therapeutic agents which have a short lifetime at the delivery sites (e.g. stomach, intestine, etc) and have to be released at the site of action in another part of the body...insulin for the treatment of diabetes, or Cop 1 (Copaxone®) for the treatment of multiple sclerosis, or antibodies such as Herceptin for the treatment of breast cancer (see paragraph [0224], and claims 39-40). Braxton patent No. '897 teaches exemplary proteins for which an increase half-life has

been accomplished by PEGylation of the protein include: hGH, **insulin**, interferon, tPA, **EPO, G-CSF…factor VIII…IgG** and so on (see column 25, lines 9-38).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru et al, Martins et al patents, Heldman et al and Braxton patent, since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V. Martin et al teach Interferon gamma, G-CSF, M-CSF, GM-CSF, and other proteins that are incorporated with the liposomes.

Furthermore, Heldman et al teach that Copaxone®, insulin, herceptin (monoclonal antibody) all have very short lifetime at the delivery site. As evidenced by www.copaxone.com, multiple sclerosis (MS) is known to be treatable by Copaxone®. Therefore, it would have been obvious to one of ordinary skill in the art to treat multiple sclerosis with a pharmaceutical composition comprising Copaxone® non-covalently bound to colloidal particle. Further, it would have been obvious to one of ordinary skill in the art to use the liposomes of Baru to increase the half life of these compounds. Therefore, one of ordinary skill in the art would have been motivated to combine the teachings, since the prior arts all teach therapeutic composition containing PEG-neutral liposome, and Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which **have a longer half-life in vivo**, because they are not removed by the RES (see p. 4, lines

1-6). Martin reference teaches that these PEG-neutral liposomes are well tolerated *in vivo* without toxic effects, and that cholesterol contributes to membrane rigidity and stability in lipid bilayer structures and be less effective in promoting liposome evasion of the RES in the bloodstream. The formulations of the prior arts are similar and they achieve the same effect (increasing the half-life of the compound). PEGylation of proteins increases half-life of these proteins, including G-CSF, interferon gamma and factor VIII (including prothrombin, factor X and so on disclosed in Baru reference), insulin, Copaxone® and antibodies (Heldman and Braxton). There is a reasonable expectation of success, since pegylation or utilizing liposomes would increase the half-life of the therapeutic compounds and by not encapsulating the compounds in the liposomes, smaller sized liposomes can be used which have a longer half-life *in vivo*. There is a reasonable expectation that other proteins and peptides known in the art would behave the same way as Factor VIII, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes proteins and polypeptide.

15. Claims 28-34, 36-42, 54, 57-60, 62-65, 67-69, 71-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baru M (WO 99/55306, filed in the IDS 2/15/2006) in view of Martin et al (US Patent No. 5,225,212) and Braxton (US Patent No. 5,766,897) and Papatheodoridis et al (Journal of Hepatology, 1999, 31: 747-750).

The teachings of Baru and Martin et al are described, *supra*. Baru further teaches a method of treating a patient suffering fro hemophilia comprising administering to said patient a

pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of coagulation factor VIII (FVIII) not encapsulated in colloidal particle. The difference between the reference and the instant claims is that the reference does not teach factor VIIa.

However, Braxton patent No. '897 teaches exemplary proteins for which an increase half-life has been accomplished by PEGylation of the protein include: hGH, **insulin**, **interferon**, tPA, **EPO, G-CSF…factor VIII…**IgG…**superoxide dimutase** and so on (see column 25, lines 9-38). Papatheodoridis et al further teaches that factor VII has the shortest half life (see p. 747, right column).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru et al, Martins et al patents, Braxton patent and Papatheodoridis reference, since Baru teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such proteins are coagulation factors such as <u>prothrombin, Factor X and Factor V</u>. Baru further teaches a method of treating hemophilia comprising administering a pharmaceutical composition comprising FVIII not encapsulated in colloidal particle. Martin et al teach Interferon gamma, G-CSF, M-CSF, GM-CSF, and other proteins that are incorporated with the liposomes, which have short half-life.

Furthermore, Braxton reference teaches proteins for which an increase half-life has been accomplished by PEGylation of the protein include: hGH, **insulin**, **interferon**, tPA, **EPO, G-CSF…factor VIII…**IgG…**superoxide dimutase** and so on (see column 25, lines 9-38).

Papatheodoridis et al further teaches that factor VII has the shortest half life (see p. 747, right column). Further, it would have been obvious to one of ordinary skill in the art to use the liposomes of Baru to increase the half life of these compounds. Therefore, one of ordinary skill in the art would have been motivated to combine the teachings, since the prior arts all teach therapeutic composition containing PEG-neutral liposome, and Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which **have a longer half-life in vivo**, because they are not removed by the RES (see p. 4, lines 1-6). Martin reference teaches that these PEG-neutral liposomes are well tolerated *in vivo* without toxic effects, and that cholesterol contributes to membrane rigidity and stability in lipid bilayer structures and be less effective in promoting liposome evasion of the RES in the bloodstream. The formulations of the prior arts are similar and they achieve the same effect (increasing the half-life of the compound). PEGylation of proteins increases half-life of these proteins, including G-CSF, interferon gamma and factor VIII (including prothrombin, factor X and so on disclosed in Baru reference), insulin, EPO, factor VIII and antibodies (Braxton). Since Factor VII is known to have the shortest half-life, one of ordinary skill in the art would have been motivated to increase the half-life of a therapeutic compound known to have the shortest half-life. There is a reasonable expectation of success, since pegylation or utilizing liposomes would increase the half-life of the therapeutic compounds and by not encapsulating the compounds in the liposomes, smaller sized liposomes can be used which have a longer half-life *in vivo*. There is a reasonable expectation that other proteins and peptides known in the art would behave the same way as Factor VIII, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes

proteins and polypeptide. Additionally, factor VIIa is in the same family of compounds as Factor VIII. Therefore, one would expect that factor VIIa would at least work the same as Factor VIII.

16. Claims 35, 61 and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baru M (WO 99/55306, filed in the IDS 2/15/2006) in view of Martin et al (US Patent No. 5,225,212) and Ishikawa et al (US Patent No. 5,824,778) and Igari et al (US Patent No. 5,534,269) as applied to claims 28-34, 36-42, 57, 59-60, 62-65, 67-68, 73-74 above, and further in view of Zalipsky S (US Patent No. 6,586,001).

The teachings of Baru and Martin et al, Ishikawa et al and Igari et al are described, *supra.* The difference between the references and the instant claims is that the reference does not teach aminopropanediol distearoyl (DS).

However, Zalipsky teaches liposomes containing PEG-substituted neutral lipopolymers provide similar circulation times to liposomes incorporating conventional, negatively charged PEG-substituted phopholipids. Further, the reference teaches that use of the uncharged lipopolymers can also present advantages in terms of interactions with cell surface and reduce leakage of charged substances (see abstract). The reference teaches different types of lipids (see Col. 3, lines 1-24) and the synthesis of PEG-Aminopropanediol distearoyl (see Example 1A).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings, since all of the protein therapeutics have short half-lives. Zalipsky teaches liposome containing PEG-substituted neutral lipopolymers containing proteins, antibodies, vitamins and so on, and the PEG-DS lipopolymer. Therefore, one of ordinary skill in the art would have been

motivated to combine the teachings, teach a need to increase the half-life of the therapeutic proteins, and therapeutic composition containing PEG-neutral liposome, and Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which have a longer half-life in vivo, because they are not removed by the RES (see p. 4, lines 1-6). Therefore, it would have been obvious to one of ordinary skill in the art to use the liposomes of Baru to increase the half life of these compounds. Martin reference teaches that these PEG-neutral liposomes are well tolerated in vivo without toxic effects, and that cholesterol contributes to membrane rigidity and stability in lipid bilayer structures and be less effective in promoting liposome evasion of the RES in the bloodstream. Both Ishikawa et al and Igari et al teach that "it has been desired to prolong the half-life of human G-CSF in the body as to enhance it s effects, as may be expected…interferons (alpha, beta, gamma)...erythropoietin and granulocyte colony-stimulating factor (G-CSF). These proteins, however, since they have generally short biological half-life, must be administered frequently, posing the significant physical burden of injection on patients. Zalipsky teaches that the neutral lipopolymers provide advantages in terms of interactions with cell surfaces. Since Baru teaches DSPE-PEG lipopolymer was successful and Zalipsky teaches PEG-DS lipopolymer was successful, one of ordinary skill in the art would have been motivated to try DS, since DS and DSPE belong to the same family, and expect that DS would be successful. Furthermore, pegylation of protein is general concept in the protein arts. There is a reasonable expectation of success, since pegylation or utilizing liposomes would increase the half-life of the therapeutic compounds and by not encapsulating the compounds in the liposomes, smaller sized liposomes can be used which have a longer half-life in vivo. There is a reasonable expectation that other

proteins and peptides known in the art would behave the same way as Factor VIII, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes proteins and polypeptide.

17. Claim 70 is rejected under 35 U.S.C. 103(a) as being unpatentable over Baru M (WO 99/55306, filed in the IDS 2/15/2006) in view of Martin et al (US Patent No. 5,225,212) and Braxton (US Patent No. 5,766,897) and Papatheodoridis et al (Journal of Hepatology, 1999, 31: 747-750) as applied to claims 28-34, 36-42, 45, 54, 57-60, 62-65, 67-69, 71-74 above, and further in view of Zalipsky S (US Patent No. 6,586,001).

The teachings of Baru, Martin et al, Braxton and Papatheodoridis et al are described, *supra*. The difference between the reference and the instant claim is that the reference does not teach aminopropanediol distearoyl (DS).

However, Zalipsky teaches liposomes containing PEG-substituted neutral lipopolymers provide similar circulation times to liposomes incorporating conventional, negatively charged PEG-substituted phopholipids. Further, the reference teaches that use of the uncharged lipopolymers can also present advantages in terms of interactions with cell surface and reduce leakage of charged substances (see abstract). The reference teaches different types of lipids (see Col. 3, lines 1-24) and the synthesis of PEG-Aminopropanediol distearoyl (see Example 1A).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Baru et al, Martins et al patents, Braxton patent and Papatheodoridis reference, since Baru teaches a pharmaceutical composition for parenteral administration comprising a

therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles, and teaches that the term "proteins or polypeptides capable of externally binding said colloidal particles" includes proteins and polypeptides which, similarly to FVIII, and non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V. Baru further teaches a method of treating hemophilia comprising administering a pharmaceutical composition comprising FVIII not encapsulated in colloidal particle. Martin et al teach Interferon gamma, G-CSF, M-CSF, GM-CSF, and other proteins that are incorporated with the liposomes, which have short half-life. Furthermore, Braxton reference teaches proteins for which an increase half-life has been accomplished by PEGylation of the protein include: hGH, **insulin**, **interferon**, tPA, **EPO, G-CSF…factor VIII…**IgG…**superoxide dimutase** and so on (see column 25, lines 9-38). Papatheodoridis et al further teaches that factor VII has the shortest half life (see p. 747, right column). Further, it would have been obvious to one of ordinary skill in the art to use the liposomes of Baru to increase the half life of these compounds. Therefore, one of ordinary skill in the art would have been motivated to combine the teachings, since the prior arts all teach therapeutic composition containing PEG-neutral liposome, and Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which **have a longer half-life in vivo**, because they are not removed by the RES (see p. 4, lines 1-6). Martin reference teaches that these PEG-neutral liposomes are well tolerated *in vivo* without toxic effects, and that cholesterol contributes to membrane rigidity and stability in lipid bilayer structures and be less effective in promoting liposome evasion of the RES in the bloodstream. The formulations of the prior arts are similar and they achieve the same effect (increasing the half-life of the compound). PEGylation of

proteins increases half-life of these proteins, including G-CSF, interferon gamma and factor VIII (including prothrombin, factor X and so on disclosed in Baru reference), insulin, EPO, factor VIII and antibodies (Braxton). Since Factor VII is known to have the shortest half-life, one of ordinary skill in the art would have been motivated to increase the half-life of a therapeutic compound known to have the shortest half-life. Zalipsky teaches liposome containing PEG-substituted neutral lipopolymers containing proteins, antibodies, vitamins and so on, and the PEG-DS lipopolymer. Therefore, one of ordinary skill in the art would have been motivated to combine the teachings, since the prior arts teach a need to increase the half-life of the therapeutic proteins, and therapeutic composition containing PEG-neutral liposome, and Baru reference teaches that when the liposomes do not encapsulate the therapeutic compound (Factor VIII), the smaller sized liposomes can be used which have a longer half-life in vivo, because they are not removed by the RES (see p. 4, lines 1-6). Martin reference teaches that these PEG-neutral liposomes are well tolerated in vivo without toxic effects, and that cholesterol contributes to membrane rigidity and stability in lipid bilayer structures and be less effective in promoting liposome evasion of the RES in the bloodstream. Zalipsky teaches that the neutral lipopolymers provide advantages in terms of interactions with cell surfaces. Since Baru teaches DSPE-PEG lipopolymer was successful and Zalipsky teaches PEG-DS lipopolymer was successful, one of ordinary skill in the art would have been motivated to try DS, since DS and DSPE belong to the same family, and expect that DS would be successful. Furthermore, pegylation of protein is general concept in the protein arts. There is a reasonable expectation of success, since pegylation or utilizing liposomes would increase the half-life of the therapeutic compounds and by not encapsulating the compounds in the liposomes, smaller sized liposomes can be used which have

a longer half-life in vivo. There is a reasonable expectation that other proteins and peptides known in the art would behave the same way as Factor VIII, since Baru shows that FVIII was successful, and non-limiting example for proteins or polypeptides capable of binding colloidal particles includes proteins and polypeptide. There is a reasonable expectation of success, since pegylation or utilizing liposomes would increase the half-life of the therapeutic compounds and by not encapsulating the compounds in the liposomes, smaller sized liposomes can be used which have a longer half-life *in vivo*. Additionally, factor VIIa is in the same family of compounds as Factor VIII. Therefore, one would expect that factor VIIa would at least work the same as Factor VIII.

Conclusion

18. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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